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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/815,778	04/02/2004	Gordana Vunjak-Novakovic	103248-010501	8172

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EXAMINER	
SINGH, SATYENDRA K	
ART UNIT	PAPER NUMBER
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/815,778	VUNJAK-NOVAKOVIC ET AL.	
	Examiner	Art Unit	
	SATYENDRA K. SINGH	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-68* is/are pending in the application.

4a) Of the above claim(s) *12-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/24/08; 5/1/08; 6/16/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response and amendments to claims filed on August 7th 2008 is duly acknowledged.

Claims 12-43 and newly added claims 44-68 are now pending in this application.

Claims 1-11 (applicant's elected invention; group Ia) have been canceled by applicant's current amendments to claims.

Claims 12-43 (as non-elected inventions) have been withdrawn from further consideration.

Newly added claims 43-68 (taken as applicant's elected invention of group Ia; directed to **a cartilage repair implant**; elected specie of additive "**growth factor**") are examined on their merits in this office action.

The following contains new grounds of rejection necessitated by applicant's current amendments to claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 44-68 (newly presented) are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Instant claims 44-47 as currently presented recite limitations "such that said bone base and said cartilage cap are **substantially free** of cellular material" (claim 44), "said cartilage cap of said decellularized plug is **substantially free** of chondrocytes" (claim 45), "said bone base and said cartilage cap of said decellularized plug are **substantially free** of pluripotent mesenchymal cells" (claim 46), and "said bone base and said cartilage cap of said decellularized plug are **substantially free** of proteoglycans" (claim 47), for which there is no explicit support or description in the instant disclosure, original claims, drawing, or the examples provided by applicants. The disclosure provided by applicants in the original claims (see for example canceled claim 1, "**said allograft bone plug having been treated to remove cellular debris and proteoglycans**"; see also specification, page 12, example 1, 1st paragraph, in particular) while providing the basis for removal of cellular debris and proteoglycans from the "bone plug", does not provide an explicit support or exemplification/disclosure for the limitations as pointed out above in new claims 44-47, in particular. In addition, applicant's remarks (filed on August 7th 2008; see page 13, in particular) fail to point out appropriate support for such limitations, which are now required by the newly presented claims. Since, the claimed invention is not fully supported by the disclosure either in the narrative or generic or in the examples or in the original claims provided by applicants, the claimed limitations constitute a **new matter** situation. Since, claims 48-68 variously depend from the broader claim 44, they are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Appropriate explanation/correction is required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 44-68 (newly presented) are rejected under 35 U.S.C. 103(a) as being unpatentable over Hart et al (US 5,782,835; [A]) in view of Stone (US 6,267,786 B1; [A2]), Peretti et al (2000; IDS) and Hoffman (2002; [U]).

Claims (interpreted herein as a product-by-process) are directed to "In a cartilage repair implant which includes an allograft bone plug having a subchondral bone base and an overlying cartilage cap, the improvement wherein said plug is decellularized such that said bone base and said cartilage cap are substantially free of cellular material, said decellularized plug including a sidewall that is sized and shaped such that a first portion of said sidewall engages a bore drilled in a cartilage defect area of host tissue and such that a second portion of said sidewall does not engage the bore, thereby forming a space between the bore and said second sidewall portion, the

improvement further comprising an allograft milled cartilage mixture, which includes a biocompatible carrier, at least partially filling the space between the bore and said second sidewall portion of said decellularized plug to thereby enhance tissue integration between said decellularized plug and adjacent host tissue." (see instant claims 45-68 for detailed recitations)

> *"[E]ven though **product-by-process claims** are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir.1985).*

Hart et al [A] (while disclosing apparatus and methods for articular cartilage repair) teach a **cartilage repair implant** (in the form of a pre-shaped bone plug; see Hart et al, abstract, summary of the invention, lines 9-14, and column 3, 4th paragraph, in particular) comprising a sterile, cylindrical shaped structure made of subchondral bone and overlying integral hyaline cartilage cap, wherein said shaped structure has been dimensioned to fit in a drilled bore in a cartilage defect (in the form of a bone plug having a functional fit within the drilled bone hole; see Hart et al, columns 7-9, column 8, lines 50-55; and figures 8-9, in particular). Additionally, Hart et al [A] explicitly suggest the use of various bio-adhesives (known in the art to fill the gap between the plug and the hole in the native tissue structure), and additives with the bone plug, such as bone or cartilage **growth-promoting factors** (see Hart et al, column 9, 2nd paragraph, lines 18-24, in particular), including cartilage-derived growth factor, various interleukins, platelet-derived growth factor (PDGF), and bone morphogenic protein (BMP).

However, a bone plug that has been "**decellularized**' such that bone base and cartilage cap are substantially free of cellular material, is not disclosed by the invention of Hart et al.

Stone [A2] while disclosing non-immunogenic, proteoglycan-reduced soft tissue xenografts teaches a process wherein the immunogenicity of tissue grafts can be reduced by chemical treatment of said grafts such as washing the skeletal tissue in saline and alcohol; subjecting the graft to cellular disruption treatments; and digesting the graft with a proteoglycan

depleting factor and/or glycosidase, and optionally following with a capping (i.e. chemical modifications of carbohydrate molecules on the surface of graft tissue) treatment in order to make the graft suitable for implantation purposes (see abstract, summary of the invention, and claims 20 and 21, in particular), wherein the soft tissue xenografts comprise a portion of subchondral bone, and wherein the graft can be implanted in to host cartilage defect site using biological adhesives such as fibrin clot or glue (i.e. polymeric carrier; see column 16, lines 45-55, in particular).

Thus, given the detailed disclosure for the benefits of decellularization of tissue grafts as taught by Stone, it would have been obvious to a person of ordinary skill in the tissue engineering art to use the process disclosed by Stone in order to successfully obtain a cartilage repair implant that has been decellularized, and is thus substantially free of cellular and other immunogenic materials such as proteoglycans for the benefits and suitability of implantation into host tissue without the risk of immune rejections.

However, a cartilage repair implant comprising an **allograft milled cartilage** mixture, which includes a **biocompatible carrier** at least partially filling the space between the bore and the sidewall portion of decellularized plug, is not explicitly disclosed by the referenced inventions of Hart et al when taken with Stone.

Peretti et al (IDS) disclose the use of cell-based tissue-engineered **allogeneic** implant material for articular cartilage repair in experimental animals, wherein the implant material comprises small pieces (lamb **articular cartilage pieces** chopped under sterile conditions, lyophilized, and sorted through two different meshes to obtain specimens between the range of **500 to 1000 microns**; see Peretti et al, abstract, page 567; Materials & Methods, page 568-572; and figure 1-2, in particular) of sterile, **minced allograft cartilage mixed in thrombin/fibrinogen solution** (i.e. a biocompatible polymeric carrier) with or without allogenic

chondrocyte cell preparation (see pages 568-569, in particular) in a buffered solution (such as buffered PBS) containing appropriate antibiotics. Peretti et al conclude and explicitly suggest that a composite of fibrin glue and sterile, milled allograft cartilage pieces can effectively serve as a scaffold for chondrocyte transplantation, preserve the original phenotype of the chondrocytes, and maintain the original mass of the implant, which may represent a valid option for addressing the problem of articular cartilage repair (see Peretti et al, abstract on page 567, and discussion on pages 574-575, in particular). The claimed limitations of milled cartilage being hyaline and/or fibrocartilage are also met by the disclosure of Peretti et al, wherein the sterile, lamb cartilage chips or small pieces are used to obtain a cell-based allogenic implant construct, as discussed above.

Therefore, it would have been obvious to a person of ordinary skill in the tissue engineering art, at the time this invention was made, to modify the decellularized cartilage repair implant of Hart et al (in view of the disclosure of Stone, as discussed above) such that the decellularized bone plug is surrounded at least partially using a mixture of milled allograft cartilage pieces or mixture in a biocompatible polymeric carrier (such as a solution containing thrombin and fibrinogen), as explicitly disclosed by the invention Peretti et al.

An artisan of ordinary skill in the art would have been motivated to modify the decellularized cartilage repair implant of Hart et al (taken with the disclosure of Stone) because the cited prior art references suggest the incorporation of chondrogenic factors (i.e. various growth factors; Hart et al above), such that it incorporates allograft milled cartilage pieces along with chondrocytes in a biocompatible carrier (Peretti et al, see discussion above) in order to effectively address the problems associated with the articular cartilage repair (i.e. by effectively

serving as an efficient scaffold for chondrocyte transplantation, preserving the original phenotype of the chondrocytes, and maintaining the original mass of the implant; see discussion, supra) with reasonable expectation of success.

However, a cartilage repair implant comprising allograft milled cartilage mixture which includes **a biocompatible carrier** such as sodium hyaluronate, gelatin, collagen, chitosan, alginate, or dextran (see recitations of instant claims 51-55 and 57, in particular), although clearly suggested (see disclosure of Hart et al, column 9, 2nd paragraph, in particular; or use of polymeric carriers such as fibrin glue, buffered PBS, etc. by Peretti et al), is not explicitly taught by the cited references of Hart et al in view of Stone and Peretti et al.

Hoffman [U] discloses the use of various types of polymeric materials and hydrogels such as hyaluronic acid, chitosan, gelatin, collagen, dextran, alginate, etc. in biomedical applications, especially for use as cell and drug carriers, and as tissue engineering matrices (see Hoffman, abstract, page 3, and table 1, in particular), wherein said polymeric materials have been shown to be useful in the field of tissue engineering as matrices and/or as bioadhesive carriers, for repairing and regenerating a wide variety of tissue and organs (see page 4, left column, 1st paragraph, right column, last paragraph, and page 9, figure 5, in particular).

Thus, to an artisan of ordinary skill in the tissue engineering art, at the time this invention was made, it would have been amply obvious to successfully substitute biocompatible polymeric carriers that have already been well known in the art, as evidenced by the detailed disclosure of Hoffamn. An artisan of ordinary skill would have been motivated to substitute biocompatible carriers to fill the space or gap between the decellularized plug (as disclosed by Hart et al in view of Stone and Peretti et al) and the sidewall, using allograft milled cartilage pieces because Hoffman clearly provides various benefits of such carriers in tissue engineering (such as for applications as porous, regenerating matrices, or for delivery of growth factors, drugs, or for

various structural advantages that effectively support growth of cells responsible for tissue regeneration, etc.).

Given the detailed teachings in the cited prior art references as discussed above, the limitations of claim 59-64 (i.e. various shapes of the allograft bone plug and diameter ranges) would have been obvious to a person of ordinary skill in the clinical art as evidenced by the fact that Hart et al disclose cylindrical grafts (see Hart et al, figure 8, column8, 2nd and 3rd paragraphs, in particular), the diameter ranges of which would have been obvious design choice depending on the type and measurement of the cartilage defects being treated. Similarly, the limitations "wherein the decellularized plug is lyophilized" to have a particular water content (see instant claims 48-49) would have been obvious to a person of ordinary skill in the tissue engineering art as evidenced by the disclosure Peretti et al that demonstrate the use of lyophilization for the preparation of milled articular cartilage specimens (see Peretti et al above). In the absence of any evidence to contrary, the shape, size, and diameter ranges of the cartilage repair implants, and the step of lyophilization to obtain the bone plug with certain water content, would have been obvious parameters for an artisan of ordinary skill in the tissue engineering art to vary and optimize depending on the parameters of the cartilage defects being treated and the stability of the decellularized bone plugs desired.

Thus, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill in the clinical art at the time the claimed invention was made.

As per MPEP 2111.01, during examination, the claims must be interpreted as broadly as their terms reasonably allow. In re American Academy of Science Tech Center, F.3d, 2004 WL 1067528 (Fed. Cir. May 13, 2004)(The USPTO uses a different standard for construing claims than that used by district courts; during examination the USPTO must give claims their broadest reasonable interpretation.). This means that the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 44-68 (newly presented) are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-42 of copending Application No. 10/438,883 (same assignee, common inventors). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the co-pending application are also directed to "a cartilage repair assembly for repair of a defect in an articular cartilage comprising a sterile allograft bone plug having a subchondral bone portion and an integral overlying cartilage cap, said allograft bone plug having been treated to remove cellular debris and proteoglycans and sized to have an interference fit in a drilled bore in a cartilage defect area and allograft milled cartilage mixed in a biocompatible carrier placed in contact with said allograft bone plug in a defect area being repaired" (see claim 1, in particular). Since the two sets of pending claims are co-extensive in scope, an ODP rejection is deemed proper.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's argument (see remarks, pages 19-20, in particular) that claims in co-pending application 10/438,883 recite "interference fit" feature, and therefore are not obvious over the instant claims 44-68 of the instant application, is not found to be persuasive because claim 1 (of

the co-pending application 10/438,883) does require cartilage repair assembly with "allograft milled cartilage mixed in a biocompatible carrier in contact with said allograft bone plug in a defect area being repaired", and thus it appears that although the claimed invention recited the limitation of "interference fit", it still remains co-extensive in scope with the claim 44 of instant application as it requires the use of milled cartilage mixture and carrier for the repair of the defect site. Moreover, instant claim 44 does not recite specific distances or space, etc. between the sidewalls and the bone plug that is being implanted with the help of milled cartilage mixture having a biocompatible carrier, and therefore, it is deemed to have an overlapping scope with the claim 1 of co-pending application 10/438,883. The ODP rejection of record, is therefore, deemed proper and is maintained.

Response to Applicant's Arguments

Applicant's arguments with respect to claims 44-68 (as they pertain to the previous prior art rejection of record) have been considered but are moot in view of the new ground(s) of rejection made in this office action.

Conclusion

NO claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SATYENDRA K. SINGH whose telephone number is (571)272-8790. The examiner can normally be reached on 9-5MF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Satyendra K. Singh/
Examiner, Art Unit 1657

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